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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,202	04/13/2006	Osamu Honmou	033873-0108	4131

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,202	HONMOU ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,9,11-15 and 17-30* is/are pending in the application.

4a) Of the above claim(s) *20-22,25 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,9,11-15,17-19,23,24 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/27/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 January 2011 has been entered.

Claim Status

Claims 6, 8, 9, 11-15 and 17-30 are pending. Claims 1-5, 7, 10, 16 are cancelled. Claim 20 is amended. However, claims 20-22, 25 and 27-30 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 6, 8, 9, 11-15, 17-19, 23-24 and 26 are under current examination.

Priority

This application claims benefit as a 371 National Stage application of PCT/JP04/09386 (filed 06/25/2004). The application also claims benefit from foreign application, JAPAN 2003-432329 (filed 12/26/2003). Accordingly, the instant application has been granted the benefit date, 26 June 2003, from foreign application, JAPAN 2003-432329.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 27 January 2011 consisting of 1 sheet(s) is/are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

RESPONSE TO ARGUMENTS

35 USC § 112

The rejections of claims 6, 8, 9, 11-15, 17-19, 23-24 and 26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements are withdrawn in response to the applicants arguments.

The applicant's claim arguments are persuasive. The specification provides support for each of: (1) a vector comprising an hTERT gene and (2) a vector having at least one of BDNF gene, PLGF gene, GDNF gene, or IL-2 gene. Therefore, a skilled artisan would understand that the specification can also encompass embodiments which are directed to a mesenchymal stem cell having both (1) a vector comprising an hTERT gene and (2) a vector having at least one of BDNF gene, PLGF gene, GDNF gene, or IL-2 gene. There is nothing in the instant specification which teaches away from combining these elements in the same cell.

Therefore, the examiner hereby withdraws the rejection of claims 6, 8, 9, 11-15, 17-19, 23-24 and 26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Tennekoon

Claims 6, 8, 9, 11, 13-14, 18-19, and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tennekoon et al. (US-6,673, 606).

Claim 6 is directed to a neurological disease therapeutic agent comprising a therapeutically effective amount of a mesenchymal stem cell as an active ingredient, wherein the mesenchymal stem cells has been treated ex vivo with a transfection vector comprising a BDNF gene, PLGF gene, GDNF gene, or IL-2 gene, and wherein the mesenchymal stem cell is an immortalized stem cell that has been treated ex vivo with a transfection vector comprising hTERT gene and a therapeutically acceptable carrier therefor.

Essentially, the structural limitations of claim 6 is directed to a mesenchymal stem cell having been transduced *ex vivo* with both (1) a vector comprising an hTERT gene and (2) a vector having at least one of BDNF gene, PLGF gene, GDNF gene, or IL-2 gene.

Tennekoon et al. teach "delivering to an MSC a vector (e.g., a retroviral construct) that contains a DNA molecule capable of encoding hTERT...Once immortalized, an MSC can be differentiated into ether an oligodendrocyte or neuronal lineage, according to the methodology disclosed herein. The invention also provides for infecting an MSC with one or more additional exogenous DNA molecules, in conjunction with h-tert." (col.13, lines 12-14, 27-33, emphasis added by examiner). Tennekoon et al. also teach, "in a further approach, DNA that encodes a growth factor or a cytokine can be transfected into MSCs...a gene that upon expression produces...brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF)" (col.14, lines 30-31, 35-38, emphasis added by examiner). Tennekoon et al. teaches that their "MSCs can be a therapeutic source, either in vitro or in vivo" (abstract). Therefore,

Tennekoon envisioned embodiments of the claimed neurological disease therapeutic agent encompassing claims 6 and 8.

Claim 9 is directed to a method for treating a neurological disease comprising administering to a patient of a therapeutically effective amount of a cranial nerve disease therapeutic agent for *in vivo* administration, comprising a mesenchymal cell as an active ingredient, wherein the mesenchymal stem cell has been treated *ex vivo* with a transfection vector comprising a BDNF gene, PLGF gene, GDNF gene, or IL-2 gene; and wherein the mesenchymal stem cell is an immortalized mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising an hTERT gene. Tennekoon teach treating patients with CNS disorders by administering their genetically modified MSCs (col.13-14).

Claim 11 is directed to the method of claim 9, wherein the neurological disease is cerebral infarction or severe cerebral infarction. Tennekoon teach treating stroke with their method (abstract).

Tennekoon further teach the limitations of claim 13 directed to wherein the MSCs are bone marrow stem cells (Example 2).

Claim 14 is directed to the method of claim 13, wherein the bone marrow stem cell is an autologous cell of the patient. The teachings of Tennekoon describe administering human MSCs to rats. However, Tennekoon suggest their invention is for human therapy. Therefore a skilled artisan would be motivated to use autologous cells in human transplant therapy. Autologous transplant therapies are known and practiced in the art and are therefore predictable. Therefore, the method as taught by

Tennekoon et al would have been *prima facie* obvious over the method of the instant application.

Claim 18 is directed to a method for neuroprotection of a neurological disease patient comprising administering to a patient in need thereof a therapeutically effective amount of a cranial nerve disease therapeutic agent for *in vivo* administration, comprising a mesenchymal cell as an active ingredient, wherein the mesenchymal stem cell has been treated *ex vivo* with a transfection vector comprising a BDNF gene, PLGF gene, GDNF gene, or IL-2 gene; and wherein the mesenchymal stem cell is an immortalized mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising an hTERT gene. Tennekoon teach treating patients with CNS disorders by administering their genetically modified MSCs (col.13-14). Additionally, Tennekoon teaches that their method promotes survival of neurons (col.14, lines 65-67).

Claim 19 is directed to a method for regenerating the cranial nerve of a neurological disease patient comprising administering to a patient in need thereof a therapeutically effective amount of a cranial nerve disease therapeutic agent for *in vivo* administration, comprising a mesenchymal cell as an active ingredient, wherein the mesenchymal stem cell has been treated *ex vivo* with a transfection vector comprising a BDNF gene, PLGF gene, GDNF gene, or IL-2 gene; and wherein the mesenchymal stem cell is an immortalized mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising an hTERT gene. Tennekoon teach treating patients with CNS disorders by administering their genetically modified MSCs (col.13-14).

Additionally, Tennekoon teaches that their method provides for differentiation of genetically modified Mesenchymal stem cells into neurons (Examples 4 and 5).

Claim 23 is directed to a method for delivering therapeutic genes to a neurological disease site of a patient with neurological disease comprising administering to a patient in need thereof a therapeutically effective amount of a cranial nerve disease therapeutic agent for *in vivo* administration, comprising a mesenchymal cell as an active ingredient, wherein the mesenchymal stem cell has been treated *ex vivo* with a transfection vector comprising a BDNF gene, PLGF gene, GDNF gene, or IL-2 gene; and wherein the mesenchymal stem cell is an immortalized mesenchymal stem cell that has been treated *ex vivo* with a transfection vector comprising an hTERT gene. Tennekoon teach treating patients with CNS disorders by administering their genetically modified MSCs comprising therapeutic genes (col.13-14).

Claim 24 is directed to the method of claim 23, wherein the neurological disease is cerebral infarction or severe cerebral infarction. Tennekoon teach treating stroke with their method (abstract).

As Tennekoon et al. does not explicitly recite a single embodiment which the examiner interprets as being anticipatory, the examiner has chosen not to reject the instant claims under 35 USC 102. However, there is teaching by Tennekook suggesting an embodiment encompassing a mesenchymal stem cell having been transduced *ex vivo* with both (1) a vector comprising an hTERT gene and (2) a vector having BDNF gene (or PLGF gene).

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to combine the teachings of Tennekoon and Zhao treat acute stage cerebral infarction with a mesenchymal stem cell having been transduced *ex vivo* with both (1) a vector comprising an hTERT gene and (2) a vector having at least one of BDNF gene, PLGF gene, GDNF gene, or IL-2 gene.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (genetically modified MSCs comprising hTERT and BDNF; using genetically modified MSCs for treating neurological disease) are taught by Tennekoon and further they are taught in various combinations. It would be therefore predictably obvious to use a combination of these elements in a method of treating neurological diseases.

An artisan would have expected success, because at the time of the filing of the instant application, mesenchymal stem cells, including genetically modified MSC were used for treating neurological diseases.

Therefore the products and methods as taught by Tennekoon et al would have been *prima facie* obvious over the method of the instant application.

Tennekoon & Zhao

Claims 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tennekoon et al. (US-6,673, 606) as applied to claims 9 and 11 above, and further in view of Zhao et al. (*Experimental Neurology*. 2002; 174: 11-20).

The teachings of Tennekoon et al. are described above in the pending 35 USC 103 rejection. In particular, Tennekoon teach treating stroke with their method (abstract), satisfying claim 11. Tennekoon does not specifically indicate that the stroke is severe (or hyperacute) cerebral infarction.

Claim 15 is directed to the method of claim 11, wherein the severe cerebral infarction is a hyper acute stage or acute stage. Zhao teach an animal model of acute cerebral infarction (stroke), creating ischemia by ligating a cerebral artery (page 12). Zhao also teach treating such animals with MSCs (page 12-13).

Claim 17 is directed to the method of claim 11, wherein the neurological disease therapeutic agent is administered to a patient at any one of the times selected from: a) after 72 hours from the onset of cerebral infarction or severe cerebral infarction; a) after 72 hours from the onset of cerebral infarction or severe cerebral infarction; b) after 24 hours from the onset of cerebral infarction or severe cerebral infarction; c) after 12 hours from the onset of cerebral infarction or severe cerebral infarction; d) after 6 hours from the onset of cerebral infarction or severe cerebral infarction; e) after 3 hours from the onset of cerebral infarction or severe cerebral infarction. Zhao et al. teach transplanting MSCs into brain of their animal model one week after ischemia was

induced (page 13, col.1, lines 5-8). One week is "after" 72 hours from the onset of cerebral infarction or severe cerebral infarction.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to combine the teachings of Tennekoon and Zhao treat acute stage cerebral infarction with a mesenchymal stem cell having been transduced *ex vivo* with both (1) a vector comprising an hTERT gene and (2) a vector having at least one of BDNF gene, PLGF gene, GDNF gene, or IL-2 gene.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (genetically modified MSCs comprising hTERT and BDNF; using genetically modified MSCs for treating stroke; using MSCs for treating acute cerebral infarction at least 3 days after onset of cerebral infarction) are taught by Tennekoon or Zhao and further they are taught in various combinations. It would be therefore predictably obvious to use a combination of these elements in a method of treating stroke.

An artisan would have expected success, because at the time of the filing of the instant application, mesenchymal stem cells, including genetically modified MSC were used for treating stroke.

Therefore the method as taught by Tennekoon et al in view of Zhao et al would have been *prima facie* obvious over the method of the instant application.

Tennekoon & Mahmood

Claims 12 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tennekoon et al. (US-6,673, 606) as applied to claims 9 and 23-24 above, and further in view of Mahmood et al. (Neurosurgery, Vol.49, No.5, November 2001: 1196-1204).

The teachings of Tennekoon et al. are described above in the pending 35 USC 103 rejection. In particular, Tennekoon teach delivering therapeutic genes in a genetically modified mesenchymal stem cell to treat neurological disease. Tennekoon suggest their genetically modified MSCs can be used to treat stroke.

Tennekoon does not specifically indicate that intravenous administration can be used to introduce the genetically modified mesenchymal stem cells to the patient.

However, Mahmood et al. teach intravenous injection of MSC for treatment of traumatic brain injury. Mahmood also generalizes that stroke (cerebral ischemia) is a type of brain injury that can be treated with MSC (page 1196, col.2, line 3; page 1200, col.2, 3rd full parag.). Furthermore, Mahmood et al.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to combine the teachings of Tennekoon and Mahmood treat cerebral infarction by intravenous administration of mesenchymal stem cells having

been transduced *ex vivo* with both (1) a vector comprising an hTERT gene and (2) a vector having at least one of BDNF gene, PLGF gene, GDNF gene, or IL-2 gene.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (genetically modified MSCs comprising hTERT and BDNF; using genetically modified MSCs for treating stroke; intravenous administration of MSCs to treat brain damage) are taught by Tennekoon or Mahmood and further they are taught in various combinations. It would be therefore predictably obvious to use a combination of these elements in a method of treating stroke or delivering genes by intravenous injection of genetically modified MSCs.

An artisan would have expected success, because at the time of the filing of the instant application, mesenchymal stem cells had been successfully delivered to the brain by intravenous injection.

Therefore the method as taught by Tennekoon et al in view of Mahmood et al would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Primary Examiner, Art Unit 1633